Remarks

Applicants are in receipt of the Office Action mailed May 6, 2005 and have the following comments.

Applicants acknowledge the Examiner's withdrawal of the previous rejections pursuant to 35 USC §112(1) and (2), and thank the Examiner for indicating that the claims are now free of §112 rejections.

REJECTIONS PURSUANT TO 35 USC §103(a)

Claims 1-6,8,9,11-13, 15 and 16 were rejected as allegedly obvious over the combination of Desantis (U.S. Patent Publication 2001/0047012) and Collins et al., (WO 01/92288). Applicants respectfully traverse this rejection for the following reasons.

A claimed invention is in violation of 35 U.S.C. §103(a) if the difference between the teachings of the prior art and of the claimed invention when taken as a whole are such that a person of ordinary skill in the art would find the claimed invention obvious in light of the prior art. *Graham v. John Deere Co.*, 148 USPQ 459 (S.Ct. 1966). Moreover, when performing this analysis, one must be cognizant of secondary considerations that "give light to the circumstances surrounding the origin of the subject matter sought to be patented". *Id.* at 467.

The present invention comprises a topical ophthalmic composition comprising a conjugated molecule comprising an EEC

and a TC. Upon topical instillation of the ophthalmic composition, the EEC not only increases the partition coefficient of the TC, but is believed to bind the retinal epithelium, thereby selectively targeting the TC to the retina. See e.g., Specification, page 11, lines 3-28.

Desantis et al. discuss the possible administration of various combinations of a) a glutamate antagonist and b) an IOP (intraocular pressure) controlling agent for the treatment of glaucoma or ocular hypertension. The list of glutamate antagonists includes 6 very broad generic structures, and all isomers and pharmaceutically acceptable salts thereof (these generic structures do not include amantidines), reference to additional compounds listed in a PCT application (WO 94/13275), and a list of 14 additional compounds. The number of glutamate antagonists listed in Desantis et al., thus number in the thousands. One of the 14 additional compounds is memantine. See Desantis et al., page 2, paragraphs [0009] through [0018].

Likewise, Desantis discloses that "the IOP-lowering agents useful in the present invention include all presently known IOP-lowering pharmaceuticals", including (without limitation) miotics, α and β adrenergic agonists, beta blockers, prostaglandins, carbonic anhydrase inhibitors. See Desantis et al., paragraph [0023]. Among such compounds is mentioned brimonidine.

Desantis et al. does not disclose, and provides no motivation for a person of ordinary skill in the art to make, a conjugated molecule comprising any of the IOP-controlling compounds or glutamate antagonists disclosed therein, much less the EEC and the TC of the present claims. Disclosure of such a

conjugated molecule comprising an EEC and a TC is entirely missing from Desantis and is found only in the present application. Indeed, one of skill in the art reading Desantis would have absolutely no reason to wish to undergo the extra work and expense of making a conjugate from two glaucoma medications, since the combination therapy disclosed therein is said to work well.

Collins et al. is directed to antibiotic agents and imaging agents, and does indeed disclose conjugates. However the conjugates of Collins comprise a cobalamin (Vitamin B_{12} derivative compound) as one moiety and an antibiotic agent as the other moiety of the conjugate. Collins states that the advantage of the conjugate is that the transcobalamin-or intrinsic factor-binding agent is a carrier for the linked antibiotic, which "localize in or near the infectious tissue, allowing efficient therapy". Collins et al., at 36, line 29. Among the hundreds of antibiotics mentioned are Symmetral syrup, and flumadine, two amantidine derivatives that are approved for use as selective antiviral (anti-influenza A) agents.

Thus, Collins does not in any way suggest the combination of amantidines with ophthalmic agents, much less motivate the person of ordinary skill in the art to make a conjugate comprising such agents.

Moreover, the combination of Desantis and Collins provides no motivation for such a person to make the presently claimed invention. Desantis is concerned solely with the treatment of glaucoma and elevated IOP. The rationale of Collins (linkage of agents to cobalamins for targeting of the active agent to

infectious tissue) would not be useful for the agents of Desantis, since such agents are not antibiotics.

Likewise, Collins is concerned with the treatment of bacterial, parasitic or viral infections. The conjugates of Collins would only be useful in ophthalmic applications (with which Desantis is exclusively concerned) for the treatment of ocular infection, and even then would involve an ophthalmologically effective antibiotic and a cobalamin (as disclosed by Collins) rather than the amantidine conjugates of the presently claimed topical ophthalmic composition. Of course, Desantis does not discuss ocular infection at all anyway, rather it is concerned only with glaucoma and elevated IOP.

The Examiner has stated that "one skilled in the art of formulation chemistry who seeks a pharmaceutical conjugate comprising a therapeutic component and an efficiency enhancing component of instant form A [apparently the amantidine structure(s) shown on page 94 of Collins] would have been motivated to prepare a formulation comprising two known therapeutically effective ophthalmic agents in a formulation that is a conjugate to treat ocular pathologies." Office Action of May 6, 2005 at page 4.

However, the Examiner has not explained why one of skill in the art would be seeking such a pharmaceutical conjugate. Indeed, the identification of "efficiency enhancing components" is only made in the present specification. Additionally, since the amantidine structure(s) shown on page 94 of Collins [formula A?]are marketed as antiviral compounds, these have not been identified as "known ophthalmic agents" in either Desantis or

Collins. Finally, as stated previously, the Examiner has provided absolutely no reason why, in light of Desantis and Collins, one of skill in the art would seek a conjugate when the combination of Desantis appears (from the teaching of Dasantis) to work perfectly well in the treatment of high IOP.

Thus, with respect, the Examiner's statement actually demonstrates that it is only by hindsight reconstruction in light of the instant specification that the Examiner can make out a case under §103 against the rejected claims. Such reconstruction is, of course, impermissible in the rejection of claims.

Finally, the Examiner states that amantidines have been described in the prior art as useful agents with poorly soluble drugs. The Examiner has not cited any references in support of this statement, and Applicants respectfully ask that, if this rejection is maintained, the Examiner make specific reference to such art of record.

However, the Applicants are aware of Tsuzuki et al., *J. Pharmaceu. Sci.* 83:481 (April 1994) and Powell et al., *Pharmaceu. Res.* 8:1418 (1991), made of record in the proecution o this application. The first of these papers disclose adamantidine esters as intravenously delivered brain-directed carriers for conjugated drugs such as AZT. The latter reference describes conjugates of admantidines with ganciclovir for topical (presumably dermal) treatment of herpes simplex and other viral infections. Neither reference describes linking amantidines with ophthalmic drugs, much less the possibility of such surprising advantages as targeting retinal epithelial

tissue by using the presently claimed topical ophthalmic compositions.

For these reasons the Applicants respectfully request the Examiner to reconsider and withdraw the rejection of the present claims under 35 U.S.C. §103(a).

Non-statutory Double Patenting Rejection

The Examiner has rejected 1-6, 8, 9, 11-12, and 14-16 under the judicially created doctrine of obviousness-type double patenting over claims 1,3-10, and 32-34 of U.S. Patent 6,562,873. Applicants hereby submit a Terminal Disclaimer over said patent which, it is thought, will obviate this rejection.

Conclusion

In conclusion, Applicants have shown that the present claims are not obvious in light of the prior art of record under 35 U.S.C. §§ 103, and have submitted a Terminal Disclaimer obviating the obviousness type double patenting rejection. Therefore, pending claims 1-12 and 14-16 are in condition for allowance, and Applicant respectfully requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the Examiner is requested to call applicant's attorney at the telephone number given below.

Respectfully submitted,

Date: 7/13/05

Carlos A. Fisher
Attorney for Applicant
Registration No. 36, 510
4 Venture, Suite 300
Irvine, California 92618
(949) 450-1750
(949) 450-1764 Facsimile